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PATENT APPLICATION SERIAL NO. _____

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PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 C.F.R. 1.53

Docket No.	IVAX0012-P2-USA	Type a plus sign (+) in this box	+

INVENTOR(s)/APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY & EITHER STATE OR FOREIGN COUNTRY)
Bodor	Nicholas	S.	Miami, Florida

TITLE OF THE INVENTION

NOVEL CYCLODEXTRIN BASED FORMULATIONS

CORRESPONDENCE ADDRESS

Dennis A. Emma, Ph.D.
IVAX CORPORATION
4400 Biscayne Boulevard
Miami, Florida 33137

ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification Number of Pages 15 ☐ Small Entity Statement

☐ Drawing(s) Number of Sheets _____ ☐ Other (specify) _____

METHOD OF PAYMENT (check one)

☐ A check or money order is enclosed to cover the Provisional filing fees	Provisional Filing Fee Amount
☒ The Commissioner is hereby authorized to charge the filing fee to Deposit Account Number: 50-0943	$160.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE Dennis A. Emma DATE: July 2, 2003

TYPED or PRINTED NAME Dennis A. Emma, Ph.D. REGISTRATION NO: 50,980

☐ Additional inventors are being named on separately numbered sheets attached hereto

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Nicholas S. Bodor
Serial No.:	To be assigned
Filing Date:	HEREWITH
Title:	NOVEL CYCLODEXTRIN BASED FORMULATIONS
Attorney Docket No.:	IVAX0012-P2-USA

CERTIFICATION UNDER 37 C.F.R. § 1.10

I hear by certify that the attached papers are being deposited with the United States Postal Service as "Express Mail Post Office to Addressee" Service of the United States Postal Service (UPS) under 37 C.F.R. § 1.10 on July 2, 2003, and is addressed to: MAIL STOP PROVISIONAL PATENT APPLICATION, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

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Angelo J Mignanelli

MAIL STOP PROVISIONAL PATENT APPLICATION
Commissioner for Patents
P.O. BOX 1450
Alexandria, VA 22313-1450

Dear Sir:

Enclosed herewith for filing with the United States Patent and Trademark Office in the above-identified Provisional Patent Application pursuant to 37 C.F.R. § 1.53 (c) are the following documents:

1. Provisional Application Cover Sheet (one page);
2. Provisional Patent Application (15 pages); and
3. Return Postcard.

Respectfully Submitted,

Dennis Emma

Dennis A. Emma, Ph.D.
Registration No. 50,980
Attorney for Applicant

IVAX CORPORATION
4400 Biscayne Boulevard
Miami, Florida 33137
Tel. No.: 305 575 6061
Fax. No.: 305 575 6064

Date: July 2, 2003

NOVEL CYCLODEXTRIN BASED FORMULATIONS

Inventor: Nicholas Bodor
(Attorney Docket: IVAX0012-P2-USA)

The invention relates to inclusion complexes of a drug and unsubstituted or substituted cyclodextrin, to pharmaceutical formulations containing the same for oral or transmucosal delivery, as well as to therapeutic uses of the same.

Oral delivery of drugs is often preferred to parenteral delivery for a variety of reasons, foremost being patient compliance, or for cost or therapeutic considerations. Patient compliance is enhanced insofar as oral dosage forms alleviate repeated health care provider visits, or the discomfort of injections or prolonged infusion times associated with some active drugs. At a time of escalating health care costs, the reduced costs associated with oral and buccal administration versus parenteral administration (requiring, at a minimum, a health care professional in the health care provider setting, with all attendant costs associated with such administration) are enhanced. In certain instances, therapeutic considerations (*e.g.*, the slow release of drug over a prolonged period) may dictate the need for oral and buccal delivery.

However, oral delivery of some active agents is plagued by poor absorption, drug lability (*e.g.*, pH dependent lability), low bioavailability, or interpatient variation. Additionally, age or the medical condition of a patient may prevent the swallowing of the oral dosage drug form thereby requiring an alternative delivery method.

Transmucosal delivery of drugs offers a means of avoiding the disadvantages of the orogastric route as the drug reaches the systemic circulation directly. The mucosal route is therefore a useful alternative comparable, if not preferred to the parenteral route, for a variety of drugs where delivery by other routes are problematic due to a variety of factors (such as for example avoidance of first pass metabolism, degradation, solubility, penetration, bioavailability, or therapeutic considerations). As exemplified herein, transmucosal delivery of drugs is an appealing route for those drugs which are acid labile. However, to date transmucosal delivery has not been possible for many drugs. Therefore, there is a need to enhance drug solubility and penetration to improve bioavailability for mucosal delivery.

The inventor has recognized that in most instances, there is an excess of cyclodextrin ("CD") present in the dosage form, which is generally used as an aid to keeping the drug in solution. However, the presence of excess cyclodextrins is suspected to inhibit drug absorption once the drug has been dissociated from the drug/cyclodextrin complex. What is required then

is a means to maximize the concentration of drug within the particular CD complex to provide the best opportunity for maximal oral or transmucosal delivery.

The inventor has discovered that using a saturated drug/CD complex solution in which the drug is in its highest thermodynamic activity state favors absorption. The saturated drug/CD complex provides the maximal amount of drug that can be solubilized with a minimal amount of cyclodextrin, thereby avoiding or minimizing absorption inhibition from an unnecessary excess of CD.

As used herein, "saturated drug/CD complex" is meant the maximum amount of drug that can be complexed with a given amount of cyclodextrin under the conditions of complexation used. The amount of drug required for saturation for a given amount of cyclodextrin may be determined empirically, such as from phase solubility studies as described *infra*.

By "mucosa" is meant the epithelial membranes lining the nasal, oral, vaginal or rectal cavities. As used herein, mucosal and transmucosal are used interchangeably. Mucosal delivery methods are well known in the art (see Remington's Pharmaceutical Sciences, 18th Ed., Gennaro, Mack Publishing Co., Easton, PA 1990 and Remington: The Science and Practice of Pharmacy, Lippincott, Williams & Wilkins, 1995). These include buccal, sublingual, tablets, lozenges, adhesive patches, gels, solutions or sprays (powder, liquid or aerosol), and suppositories (*e.g.*, for rectal or vaginal administration).

The oral drug forms contemplated by the invention include saturated drug/CD complexes and pharmaceutically acceptable inert ingredients, *e.g.*, conventional excipients, vehicles, fillers, binders, disintegrants, solvents, solubilizing agents, sweeteners, coloring agents and any other inactive ingredients, which are regularly included in pharmaceutical dosage forms for oral administration. Suitable oral dosage forms include tablets, capsules, caplets, gelcaps, pills, liquid solutions, suspensions or elixirs, powders, lozenges, micronized particles and osmotic delivery systems.

The oral dosage form, for example a conventional tablet, according to the invention will dissolve, releasing the drug/CD complex followed by dissociation of the drug from the cyclodextrin. The saturated drug/CD complex provides a minimal amount of CD necessary to solubilize the drug, thereby minimizing the potential that the dissociated drug will recomplex with CD. Minimizing complex reformation (*e.g.*, shifting the equilibrium towards dissociation) is believed to aid in avoiding or minimizing absorption inhibition from the now uncomplexed CD.

The drug/CD complex according to the invention may be formulated for transmucosal delivery. Hence, for example a buccal tablet according to the invention, upon dissolution in the

small volume of saliva present produces a saturated drug solution in which the drug is in its highest thermodynamic activity (*i.e.*, the solution contains the highest concentration of drug possible that can be complexed in the given CD) for maximizing drug delivery. One of skill in the art will appreciate that the same result may be achieved by using a variety of delivery methods, some of which do not require dissolution (*e.g.*, drug/CD complex saturated liquid preparations put in direct contact with the mucosal tissue).

Cyclodextrins are well known and are named by the number glucopyranose units in the cyclic ring (for a general overview see for example, Uekama *et al.*, in CRC Critical Reviews in Therapeutic Drug Carrier Systems, vol. 3(1), 1-40 (1987)).

Commonly used cyclodextrins include α, β, and γ cyclodextrin and derivatives thereof, in particular, derivatives wherein one or more of the hydroxy groups are substituted, *e.g.* by alkyl, hydroxyalkyl, carboxyalkyl, alkylcarbonyl, carboxyalkoxyalkyl, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl or hydroxy-(mono or polyalkoxy) alkyl groups, wherein each alkyl or alkylene moiety preferably contains up to six carbons. Substituted cyclodextrins which can also be used in the invention include polyethers, *e.g.* as described in U.S. Pat. No. 3,459,731. Further examples of substituted cyclodextrins include ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-6} alkyl, hydroxy C_{1-6} alkyl, carboxy- C_{1-6} alkyl or C_{1-6} alkyloxycarbonyl- C_{1-6} alkyl groups or mixed ethers thereof. In particular, such substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-3} alkyl, hydroxy- C_{2-4} alkyl or carboxy- C_{1-2} alkyl or more particularly by methyl, ethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxymethyl or carboxyethyl. The term "C_{1-6} alkyl" is meant to include straight and branched saturated hydrocarbon radicals, having from 1 to 6 carbon atoms, such as methyl, ethyl 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like. Of particular utility in the present invention are the β-cyclodextrin ethers, *e.g.* dimethyl-β-cyclodextrin as described in Drugs of the Future, Vol. 9, No. 8, p. 577-578 by M. Nogradi (1984) and polyethers, *e.g.* hydroxypropyl-p-cyclodextrin and hydroxyethyl-β-cyclodextrin. Besides simple cyclodextrins, branched cyclodextrins and cyclodextrin polymers may also be used. Other cyclodextrins are described for example in Chemical and Pharmaceutical Bulletin 28: 1552-1558 (1980), Yakugyo Jiho No. 6452 (28 March 1983), Angew. Chem. Int. Ed. Engl. 19: 344-362 (1980), U.S. Pat. No. 3,459,731, EP-A-0,149,197, EP-A-0,197,571, U.S. Pat. No. 4,535,152, WO-90/12035 and GB-2,189,245. Other references describing cyclodextrins for use in the compositions according to the present invention, and which provide a guide for the preparation, purification and analysis of cyclodextrins include the following: "Cyclodextrin Technology" by Jozsef Szejtli, Kluwer

Academic Publishers (1988) in the chapter Cyclodextrins in Pharmaceuticals; "Cyclodextrin Chemistry" by M. L. Bender et al., Springer-Verlag, Berlin (1978); "Advances in Carbohydrate Chemistry", Vol. 12, Ed. by M. L. Wolfrom, Academic Press, New York in the chapter The Schardinger Dextrins by Dexter French at p. 189-260; "Cyclodextrins and their Inclusion Complexes" by J. Szejtli, Akademiai Kiado, Budapest, Hungary (1982); I. Tabushi in Acc. Chem. Research, 1982, 15, p. 66-72; W. Sanger, Angewandte Chemie, 92, p. 343-361 (1981); A. P. Croft and R. A. Bartsch in Tetrahedron, 39, p. 1417-1474 (1983); Irie et al. Pharmaceutical Research, 5, p. 713-716, (1988); Pitha et al. Int. J. Pharm. 29, 73, (1986); DE 3,118,218; DE-3,317,064; EP-A-94,157; U.S. Pat. No. 4,659,696; and U.S. Pat. No. 4,383,992.

One of skill in the art will appreciate that the choice of a specific cyclodextrin will vary upon the route of administration, the drug of choice, *etc.* In certain embodiments, envisaged cyclodextrins include 2-hydroxypropyl-β-CD, 2-hydroxypropyl-γ-CD, γ-CD, βCD, or sulfobutylcyclodextrins (see *e.g.*, U.S. Pat. Nos. 5,134,127 and 6,046,177).

Solid mixtures of the cyclodextrins with the active ingredient may be prepared by a variety of methods known to those of skill in the pharmaceutical arts, such as for example, via melt-extrusion (see *e.g.*, WO97/18839, hereby incorporated by reference). However, melt-extrusion may not be appropriate for all drugs or cyclodextrins inasmuch as the melting point for some active compounds may be at a temperature which can cause decomposition of the cyclodextrins.

It is possible in certain instances to have cyclodextrin in excess in these formulations, as the optimal drug/CD complex has not been formed prior to incorporation.

Oral and transmucosal delivery forms are optionally formulated in a pharmaceutically acceptable vehicle with any of the well-known pharmaceutically acceptable carriers, including diluents and excipients (see Remington's Pharmaceutical Sciences, *supra*).

In an aspect of the invention, the drug/CD complex is a saturated drug/CD complex prepared prior to incorporation into the final drug form. A method envisioned for preparing a solid saturated drug/CD complex entails lyophilization of the complex from the complexion solution. However, those of skill in the art will appreciate alternative methodologies for preparing a solid saturated drug/CD complex.

In certain instances, oral or mucosal absorption may be further facilitated by the addition of various excipients, additives, *etc.* (to increase solubility or to enhance penetration), by the modification of the microenvironment (to favor the un-ionized form of the drug), or by the addition of mucoadhesive excipients (to improve contact between the delivery system and the mucosal tissue).

In some embodiments of the invention, the drug form is prepared with the minimal amount of excipient(s) necessary for shaping and producing the particular drug form (e.g. tablet, patch, *etc*). In this embodiment, the excipients are chosen from those that do not interfere with cyclodextrin or with complex formation. In yet other embodiments, excipient(s) are chosen from those which complex with cyclodextrins, *e.g*, to facilitate dissolution of the drug/CD complex.

The invention is useful for the administration of any drug capable of (a) oral delivery by conventional routes, and (b) capable of forming a complex with CD.

In certain embodiments, the invention is particularly useful for the administration of any drug capable of (a) transmucosal delivery, and of (b) forming a complex with CD.

Accordingly, the methods, formulations and pharmaceutical compositions described herein offer novel therapeutic modalities for the treatment of patients in need of treatment with the drug of choice. As such, the invention avoids the problems of poor absorption and bioavailability associated with oral drug dosing by providing a drug in its highest thermodynamic activity (*i.e*, the solution contains the highest concentration of drug possible that can be complexed in the given CD) for maximizing drug delivery via the orogastric route. Additionally, where necessary for some drugs, the orogastric route may be avoided entirely by transmucosal delivery.

To exemplify the advantages offered by the instant approaches, the non-limiting and representative example provided herein involves cladribine ("2-CdA"), a suspected acid labile drug. Cladribine is known as an antileukemic agent, (*i.e*, in treating leukemias, such as, hairy cell leukemia and L 1210 leukemia), as an immunosuppressive agent, and as a modality useful for the treatment of rheumatoid arthritis and multiple sclerosis (see e.g, Liliemark, J., *et al.*, Clin. Cancer Res., 1:385-390, 1995). In some studies, oral cladribine is plagued by the combination of relatively low bioavailability combined with sub-optimal interpatient variation. (See *e.g*, J. Liliemark in Clin. Pharmacokinet. 32(2): 120 -131, 1997). These art recognized problems are addressed by the instant invention and exemplified below.

Example 1
Phase Solubility Studies

Several processes for preparing cladribine are known in the art (see for example, European Patent Application No. 173,059 A2 and Robins *et al.*, J. Am. Chem. Soc., 106, 6379 (1984), and U.S. Pat. No. 5,208,327).

Various concentrations of cladribine were dissolved in hydroxypropyl-β cyclodextrin (HPβCD), HPβCD with 0.1% hydroxypropyl methylcellulose (HPMC), or γ cyclodextrin (γCD) according to the Table I.

Table I

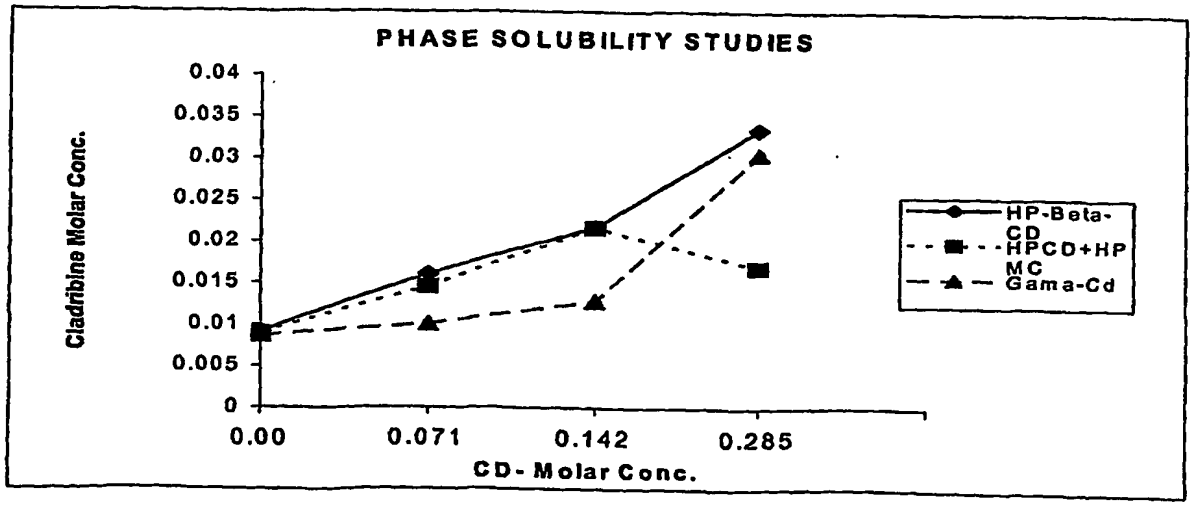
Phase Solubility Studies

CD Conc.	Cladribine –HP betaCD (Trial A)			Cladribine -HP betaCD + HPMC(0.1%) (Trial B)			Cladribine -gama- CD (Trial C)		
CD Conc.	Absorbance	mg/ml	Molar concn.	Absorbance	mg/ml	Molar concn.	Absorbance	mg/ml	Molar concn.
0.00	0.140	2.610	0.0091	0.137	2.550	0.0089	0.132	2.459	0.0086
0.018	0.169	3.139	0.011	0.146	2.711	0.0095	0.1352	2.519	0.0088
0.035	0.191	3.554	0.0124	0.175	3.262	0.0114	0.1531	2.852	0.0100
0.071	0.245	4.570	0.016	0.223	4.149	0.0145	0.1542	2.873	0.0101
0.142	0.333	6.211	0.0217	0.332	6.185	0.0216	0.1965	3.661	0.0128
0.285	0.514	9.581	0.0335	0.259	4.831	0.0169	0.4688	8.733	0.0306

Methods of preparing drug/CD complex preparations are well known in the art (see *supra*). In the instant example, a saturated solution of cladribine was prepared by mixing excess cladribine with a 40% solution of the various CDs. Undissolved cladribine was removed by filtration. The resultant solution was then lyophilized and used to make solid forms.

The molar concentration of cladribine in these solutions was then plotted and is presented graphically as Figure 1. The plotted line represents maximal drug solubilization for the conditions tested, that is, the ratio of drug to cyclodextrin for highest thermodynamic activity. The area above the plotted lines represents conditions where excess insoluble drug, here cladribine, is present. The area below the plotted line represents the conditions where cyclodextrin is in excess.

Figure 1



If there is a linear plot for the drug/complex tested, concentrating (or evaporating the frozen solution in vacuum) any of the solutions to dryness results in the unique mixture representing the maximum drug concentration that can be incorporated into the cyclodextrin under those conditions. The dried drug/cyclodextrin complex can be used to produce a tablet with a minimum of additives, such as, for example, 1% magnesium stearate or PEG, with a small amount of sorbitol. When this type of tablet is used for transmucosal delivery and undergoes dissolution, for example, in the buccal area or sublingually, the dissolution produces the saturated drug solution of highest thermodynamic activity. This complex has the best chance of penetrating the mucosal tissue. Accordingly, solutions such as the one exemplified herein are expected to facilitate transmucosal absorption.

However, a nonlinear drug/CD solubilization plot indicates multiple drug/CD complexes. The phase solubility data may then be used to identify specific drug/CD ratios for use in the particular drug form.

Example 2
Pharmacokinetic Studies

The bioavailability of cladribine, when complexed with Gamma-CD or HPCD was evaluated in a beagle dog model. The data obtained from this model are expected to be representative for the human experience.

Cladribine was complexed with either hydroxypropyl-β-cyclodextrin (HPCD) or γ-cyclodextrin (Gamma-CD) by the following method.

An aqueous solution of cladribine, in excess, and CD was mixed with stirring at 44 - 50°C for nine hours. Excess, non-complexed cladribine was removed by filtration and the solution cooled to room temperature. The aqueous cladribine/CD complexes were taken to dryness by lyophilization prior to incorporation into the solid buccal or oral tablets. The lyophilization procedure consists of rapidly bringing the complexation solution to -45°C (ca. 200 min.) followed by lyophilization at -25°C for approximately 80 – 90 hours.

Buccal and oral tablets according to the formulas presented in Table II below were prepared by blending the lyophilized drug/cyclodextrin complex (containing 5 mg of cladribine) with magnesium stearate for 10 minutes at 12 rpm. The resultant mixture was screened through

a # 18-mesh screen followed by a second blending for 5 minutes at 12 rpm and screening. The resulting blend was then compressed into 100 mg tablets using a Manesty F3 single station punch. The physical properties of the tablets produced were:

Diameter: 10 mm. Upper shallow concave tooling, lower flat beveled edge tooling

Average weight:	237mg – Gamma-CD,	217mg - HPCD
Hardness:	4.0 Kp –Gamma-CD,	3.72 Kp - HPCD
Friability:	0.5%	0.4%
Thickness:	3.8mm	3.3mm
Disintegration:	6-8min	6-8min

Table II

Representative Drug Formulations

	Placebo (% w/w)	HPCD (% w/w)	Gamma-CD (% w/w)
Drug Complex		99.0 (contains 4.95 mg cladribine)	99.0 (contains 4.96 mg cladribine)
Magnesium stearate	1.0	1.0	1.0
Gamma-CD (uncomplexed)	96.8		
Sorbital	2.2		
Total	100.0	100.0	100.0

Bioavailability and pharmacokinetic studies were conducted in a beagle dog model as follows.

Outbred male beagle dogs obtained from IDRI (Dunakeszi, Hungary) were housed in the animal facility at the IVAX Institute for Drug Research, Hungary, and allowed laboratory diet and water *ad libitum*. The same dogs were used throughout the study to minimize inter and intra subject variability.

The bioavailability and pharmacokinetic studies were conducted as follows. In the first test period, cladribine was administered intravenously (5 mg, 0.25 mg/ml in isotonic saline) and blood samples collected at various time intervals over 48 hours. In the second test period, half of the test subjects received buccally either a Gamma-CD or HPCD tablet (see Table II *supra*); with serial blood samples collected over 48 hours. The third test period repeated the second test period with the exception that the subjects previously receiving Gamma-CD were now given

HPCD buccal tablets, with HPCD recipients from the second period receiving Gamma-CD buccal tablets. The fourth and fifth test periods repeated test periods two and three with the exception that the tablets were given orally.

Cladribine levels in the blood were measured by HPLC and an LC/MS/MS method. The TopFit 2.0 Pharmacokinetic and Pharmacodynamic Data Analysis System was used for the pharmacokinetic analysis of the data. The results of the bioavailability study for control (intravenous) and cladribine/CD complexes are presented in Tables III – VII and summarized in Table VIII.

CLADRIBINE PHARMACOKINETIC PARAMETERS IN MALE DOGS
Table III

	Intravenous bolus, 5 mg cladribine/animal											
	Cinitial	Cfirst	t1/2terminal	AUD	AUDext.	AUC	Cltot	MRTtot	Body weight	dose	AUC/dose	Cltot/kg
dog	[ng/ml]	[ng/ml]	[h]	[ng*h/ml]	[%]	ng*h/ml]	ml/min	[h]	[kg]	[mg/kg]		[ml/min/kg]
PM01	655	560	10,4	426	1,4	432	193	1,3	10,98	0,46	949	17,6
PM02	525	446	8,5	337	1,4	342	244	1,2	13,86	0,36	948	17,6
PM03	726	605	10,7	426	1,5	433	192	1,3	12,44	0,40	1077	15,4
PM04	569	477	11,0	379	1,4	383	217	1,4	11,98	0,42	918	18,1
PM05	335	306	11,3	334	1,0	338	247	1,5	14,28	0,35	965	17,3
PM06	567	478	9,9	359	1,9	366	228	1,3	12,94	0,39	947	17,6
Mean	563	479	10,3	377	1,4	382	220	1,3	12,75	0,40	967	17,3
S.D.	133	103	1,0	41	0,3	42	24	0,1	1,22	0,04	56	0,9
CV%	24	22	9,8	11	20	11	11	9	10	10	6	5

Table IV

Buccal administration 5 mg cladribine/animal Tablet-1: Gamma-CD complex (RDT-0418/C)											
	Cmax	Tmax	t1/2terminal	AUD	AUDext.	AUC	MRTtot	Body weight	dose	AUC/dose	F
dog	[ng/ml]	[h]	[h]	[ngh/ml]	[%]	ngh/ml]	[h]	[kg]	[mg/kg]		[%]
PM01	31,1	4,0	15,1	115	1,8	117	6,7	12,16	0,41	285	30,0
PM02	78,8	2,0	16,9	159	1,2	161	4,2	14,72	0,34	474	50,0
PM03	107,0	2,0	21,5	214	1,6	218	4,6	12,50	0,40	545	50,6
PM04	37,3	1,5	13,3	96	1,0	97	4,2	13,02	0,38	253	27,5
PM05	30,7	3,0	9,2	92	0,4	93	4,9	15,52	0,32	289	29,9
PM06	65,4	3,0	13,2	108	0,7	109	4,5	14,40	0,35	314	33,1
Mean	58,4	2,6	14,9	131	1,1	133	4,8	13,72	0,37	360	36,9
S.D.	30,9	0,9	4,1	47	0,5	48	1,0	1,35	0,04	120	10,6
CV%	53	36	28	36	48	37	20	10	10	33	29

Table V

Buccal administration; 5 mg cladribine/animal Tablet-2: HPCD complex (RDT-0418/D)											
	Cmax	Tmax	t1/2terminal	AUD	AUDext.	AUC	MRTtot	Body weight	dose	AUC/dose	F
dog	[ng/ml]	[h]	[h]	[ngh/ml]	[%]	ngh/ml]	[h]	[kg]	[mg/kg]		[%]
PM01	78,0	2,0	10,9	128	0,5	129	3,7	12,32	0,41	318	33,5
PM02	95,6	0,8	13,8	102	1,3	103	3,7	14,96	0,33	308	32,5
PM03	54,0	2,0	9,1	106	0,6	107	4,7	12,90	0,39	276	25,6
PM04	51,5	1,0	15,5	120	0,8	121	3,3	12,74	0,39	308	33,6
PM05	*50,9	*0,75	13,9	*83	*0,6	*84	*2,88	15,08	0,33	*253	*29,6
PM06	33,4	2,0	13,1	84	1,4	85	5,3	13,68	0,37	233	24,6
Mean	62,5	1,6	12,7	108	0,9	109	4,1	13,61	0,37	289	30,0
S.D.	24,4	0,6	2,3	17	0,4	17	0,8	1,18	0,03	35	4,5
CV%	39	40	18	16	44	16	20	9	8	12	15

*: excluded from mean

Table VI

Oral administration; 5 mg cladribine/animal
Tablet-1: Gamma-CD complex (RDT-0418/C)

	Cmax	Tmax	t1/2terminal	AUD	AUDext.	AUC	MRTtot	Body weight	dose	AUC/dose	F
dog	[ng/ml]	[h]	[h]	[ngh/ml]	[%]	ngh/ml]	[h]	[kg]	[mg/kg]		[%]
PM01	218,9	0,8	11,0	193	0,4	194	2,6	12,70	0,39	493	51,9
PM02	141,2	0,5	10,2	156	0,3	156	2,3	15,08	0,33	470	49,6
PM03	234,9	0,3	13,3	214	0,4	215	1,9	13,18	0,38	567	52,6
PM04	99,6	2,0	16,2	172	0,8	174	3,5	13,18	0,38	459	50,0
PM05	*17,6	*1,5	*10,2	*52	*2	*53	*3,29	15,52	0,32	*165	*17,0
PM06	161,8	0,3	11,1	148	0,4	148	2,1	14,52	0,34	430	45,4
Mean	171,3	0,8	12,4	177	0,5	177	2,5	14,03	0,36	484	49,9
S.D.	55,8	0,7	2,4	27	0,2	27	0,6	1,16	0,03	52	2,8
CV%	33	97	20	15	42	15	25	8	8	11	6

*: excluded from mean

Table VII

Oral administration; 5 mg cladribine/animal
Tablet-2: HPCD complex (RDT-0418/D)

	Cmax	Tmax	t1/2terminal	AUD	AUDext.	AUC	MRTtot	Body weight	dose	AUC/dose	F
dog	[ng/ml]	[h]	[h]	[ngh/ml]	[%]	ngh/ml]	[h]	[kg]	[mg/kg]		[%]
PM01	143,3	0,5	12,8	174	0,5	175	2,3	12,72	0,39	445	46,9
PM02	86,9	1,5	10,6	121	0,5	122	3,4	15,00	0,33	366	38,6
PM03	231,5	0,3	12,6	199	0,4	200	2,0	13,24	0,38	530	49,2
PM04	114,3	1,5	15,0	171	0,8	172	3,7	13,16	0,38	453	49,3
PM05	147,5	1,0	14,2	149	0,7	150	3,2	15,32	0,33	460	47,6
PM06	68,5	0,5	16,9	121	0,9	123	2,8	14,32	0,35	352	37,2
Mean	132,0	0,9	13,7	156	0,6	157	2,9	13,96	0,36	434	44,8
S.D.	57,7	0,5	2,2	31	0,2	31	0,6	1,07	0,03	66	5,4
CV%	44	62	16	20	31	20	22	8	8	15	12

Table VIII

	Bioavailability of cladribine in dogs dose: 5 mg cladribine/animal			
	Gamma-CD complex		HPCD complex	
dog	Buccal	Oral	Buccal	Oral
PM01	30,0	51,9	33,5	46,9
PM02	50,0	49,6	32,5	38,6
PM03	50,6	52,6	25,6	49,2
PM04	27,5	50,0	33,6	49,3
PM05	29,9	*17,0	**29,6	47,6
PM06	33,1	45,4	24,6	37,2
Mean	36,9	49,9	30,0	44,8
S.D.	10,6	2,8	4,5	5,4
CV%	29	6	15	12

excluded from mean
*: not characteristic for the group
**: the dog probably swallowed the tablet